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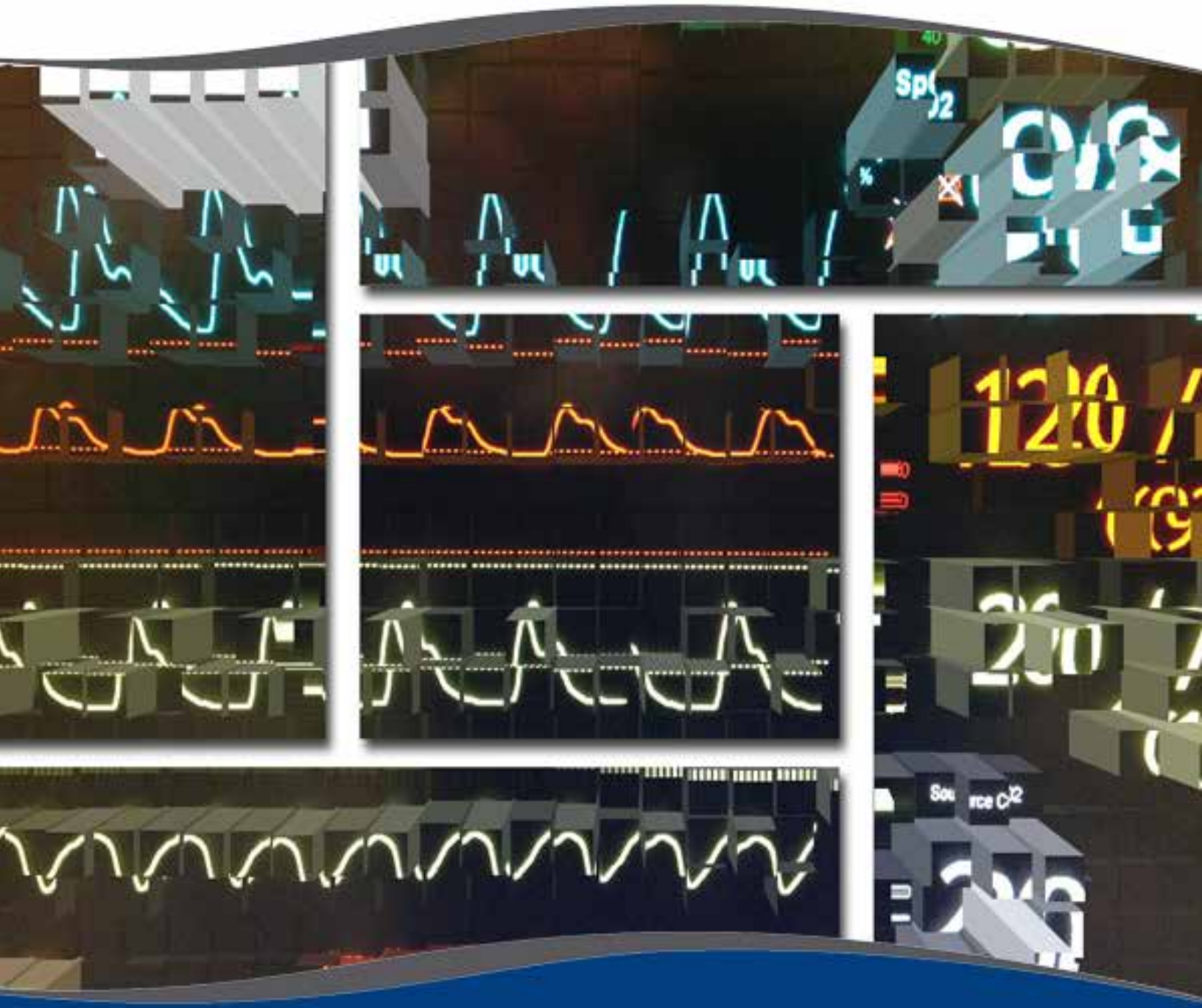

Anesthetic Considerations For The Patient With Hemophilia A

Jennifer Hopkins BSN, University of Missouri-Kansas City 2012

Continuing Education eJournal

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Disclosure: Submitted to the School of Health Professions and The Graduate Faculty of the University of Kansas In partial fulfillment of the requirements for the degree of Doctor of Nurse Anesthesia Practice

Learning Objectives

1. *Describe the pathophysiology of hemophilia A and associated patient treatments*
2. *Identify specific anesthesia considerations for the patient with hemophilia A in the perioperative period.*
3. *State the definition, incidence, and treatment of inhibitor development in the patient with hemophilia A.*

INTRODUCTION

Hemophilia A, although rare, is the most common of the inherited bleeding disorders.[1] Historically, patients who suffered from hemophilia were considered high risk (for fear of uncontrolled bleeding) and frequently denied surgical procedures.[2] Advances in medicine have increased the safety and efficacy of treatment for the patient with hemophilia, and major surgical procedures are now performed. Reducing the risk of bleeding is the primary goal of the management of hemophilia A. Additionally, specific considerations include musculoskeletal concerns, inhibitor development/management, and transfusion related illness. Anesthesia providers should be aware of the current treatments and recommendations for the patient with hemophilia A in order to provide evidence based care.

Case Report

A 60 year-old patient, with a known history of hemophilia A, presented for a decompressive lumbar laminectomy with fusion of two levels (L3-4 and L4-5). The patient's presenting symptom was bilateral radiculopathy to the lower extremities, which prompted surgical intervention. The patient also had a past medical history of human immunodeficiency virus (HIV), hepatitis C, coronary artery disease, and non-Hodgkin's lymphoma. Previous surgical history included multiple elbow procedures, cardiac stent placement, and liver biopsy. The patient reported a history of excess bleeding after both the elbow procedures and liver biopsy. This patient was seen in a pre-anesthesia clinic several weeks before the scheduled procedure. A thorough history and physical assessment were conducted. The patient underwent cardiac evaluation that revealed a negative stress test and a left ventricular ejection fraction (LVEF) of 77 %. Current home medications included NUWIQ, a recombinant Factor VIII, 3500 units IV twice weekly. During the pre-operative assessment and testing in clinic, hematology was consulted and recommendations for management were received. The recommendations from hematology stated that the patient should receive his last as scheduled dose of NUWIQ 48 hours before admission to the hospital. On admission, orders were as follows:

Preoperative	Post Operative	Discharge
3,500 Units IV immediately before surgery	3,500 Units IV every 12 hours to maintain trough* level of 50-100% * Trough: 12 hours post-dose administration	2,500 Units IV daily x 5 days *then* 3,500 Units IV every other day x 4 doses *then* Return to pre-procedure dosing schedule

The patient's baseline vital signs the day of surgery were as follows: blood pressure 120/88, heart rate 88 bpm, and oxygen saturation of 100 %. The evening prior to the surgery, Factor VIII level was 6%. Two weeks before surgery the patient's hemoglobin was 13.6 g/dl, hematocrit 39.7 %, platelets 217 x 10^9/L, and WBC's 12.7 x 10^9/L. Intravenous access was acquired, and the prescribed 3500 units of NUWIQ IV were administered to the patient. He was subsequently taken into the operating room. General anesthesia was induced with fentanyl, propofol, and succinylcholine IV. In this case a large dose of non-depolarizing neuromuscular blockade was contraindicated because intraoperative monitoring of somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs) were planned. An arterial line was placed in the radial artery after induction via ultrasound in order to facilitate continuous monitoring of blood pressure and intraoperative blood sampling. Intraoperatively, the patient remained hemodynamically stable with no acute events noted. The total blood loss was estimated at 450 ml. The patient received a cell salvage volume of 127 ml, 500 ml of albumin 5 %, and a crystalloid volume of 3100 ml. Vital signs throughout the case were systolic blood pressure 95- 140, heart rate 60- 90 bpm, pulse oximetry 95-100 % and normothermic temperatures throughout the case. General anesthesia was maintained with 0.6% isoflurane, and intravenous infusions of ketamine (200 mcg/kg/hr), fentanyl (3 mcg/kg/hr), and rocuronium (2-5 mg/kg/hr). The surgical procedure was completed as planned without incident and intraoperative time was approximately 5.5 hours. The patient met standard criteria for extubation and was extubated in the OR.

Post-operatively the patient was transferred to the intensive care unit (ICU) for continued monitoring. No unforeseen events were noted in the post-operative course and inpatient admission. The patient was followed by hematology service throughout the admission. He had frequent monitoring of Factor VIII levels (values ranged from 35-123%) as well as routine labs daily and as needed. The post-operative hemoglobin reached a nadir of 7.9 g/dl and the patient was subsequently transfused one unit of packed red blood cells (PRBCs). All other labs were within expected limits. The patient was discharged on postoperative day (POD) 5 with a hemoglobin level of 8.6 g/dl.

Pathophysiology

Hemophilia A is a rare disorder that affects 1 in every 5000 live male births[3,] and has been recognized as early as the 2nd century in males that bled excessively from circumcision.[4] Hemophilia A is an X-linked recessive disorder and correspondingly affects primarily the male gender. The expression of the inherited gene causes deficient production of Factor VIII, which leads to the prolonged bleeding characterized by this disorder. Recall that Factor VIII is part of the intrinsic pathway of the clotting cascade, and directly affects Factor X when activated. The position of Factor VIII in the clotting cascade will cause the hemophiliac to have prolonged partial thromboplastin time (PTT) and normal prothrombin (PT). Barring other pathology, platelet levels should be within normal limits as well. Because several distinctive gene mutations can disturb Factor VIII, varying severities of hemophilia A are expressed. The classification of severity of the disease corresponds to plasma level (measured in % activity) of Factor VIII and is accepted as follows: Severe < 1%, Moderate 1-4 %, and Mild > 4 %.[3]

Patients are treated for hemophilia A according to disease severity and bleeding occurrence. Bleeding episodes can be spontaneous or as a result of trauma. The World Federation of Hemophilia (WFH) describes multidisciplinary guidelines for the management of hemophilia. The goal of treatment in the hemophiliac is to prevent and treat any episodes of bleeding with specific factor replacement when possible. Patients who suffer from hemophilia may be on lifelong continuous therapy of a Factor replacement.[5] The high cost of factor replacement therapy can be an obstacle for adequate treatment; the cost of maintenance therapy in a pediatric patient has been estimated at over $100,000 per year.[3]

Bleeding in the patient with hemophilia commonly occurs into soft tissues and joint spaces (hemarthroses or hemophilic arthropathy). The joints most commonly affected by arthropathy include the knees, elbows, ankles, shoulders, wrists, and hips. Less common manifestations of bleeding in the hemophiliac include bleeding along the gastrointestinal or genitourinary tracts, and even more rare, intracerebral hemorrhage.[4] Hemophilic arthropathy may be first identified in pediatric patients as they begin to walk[6], and only when prophylaxis is initiated before the age of 4 does treatment spare normal joint function.[7] Hemarthroses can be severe and debilitating, potentially progressing to a point where surgical intervention (such as joint replacement) is the only avenue for continued mobility. Anesthesia providers may encounter hemophilia A patients most frequently in the setting of orthopedic intervention.

Anesthetic Management of the Hemophiliac

Anesthetic management of the patient with hemophilia A will ideally begin with a visit to a preoperative testing clinic, which allows for ample time and resources for optimization. A thorough pre-anesthetic evaluation is essential. Adult patients and parents of children with hemophilia will likely be well educated regarding the disease and their treatment. Severity of the disease (mild, moderate, severe) will guide Factor replacement. Management of Factor replacement by a hematologist, as in the presented case, is recommended. The patient with hemophilia may or may not be on continuous replacement of Factor VIII depending on disease severity. In the presented case, the patient was on a scheduled bi-weekly intravenous dose of NUWIQ, and this same brand of recombinant Factor VIII was continued during the perioperative course. Pre-operative assessment in the clinic allows time for the consultation of the hematologist and acquisition of prescribed treatments (factor replacement, blood products, etc.).

Inhibitor development occurs in approximately 4%-30% of patients with hemophilia A.[1] Inhibitors are antibodies that neutralize Factor VIII derivatives and can render the disease more difficult to manage, putting the patient at a higher risk for bleeding. An inhibitor assay may be conducted to diagnose the presence of these antibodies. Although a previous systematic review cited a link between surgery (coupled with factor concentrate treatment) and the development of inhibitors[8]; the cause of inhibitor development is now thought to be multifactorial. Triggers can include the patient's immune response, treatment type, and length of exposure to exogenous factor[9]. The perioperative treatment for the patient with hemophilia A and inhibitors may include higher doses of Factor VIII replacement, or agents that bypass Factor VIII in the cascade. Administration of Factor Eight Inhibitor Bypassing Activity (FEIBA), or recombinant activated Factor VII (rFVIIa) would serve useful in the presence of severe inhibitor activity.[10] If the severity of the inhibitors dictates the necessity of bypassing agents, it has been recommended that the patient procedure be conducted in a "comprehensive care" center. Comprehensive care centers, as defined by the World Federation of Hemophilia, include a multidisciplinary team consisting of a hematologist, nurse, physiotherapist, laboratory specialist, and a psychosocial expert with experience or training with hemophilia.[11]

Several comorbidities are common among those with hemophilia A. The clinician should evaluate for transfusion related disease in patients with hemophilia over the age of 50. A documented history of frequent blood or blood product transfusion is common in this population. Donated blood was not regularly tested for Hepatitis B until 1971, human immunodeficiency virus (HIV) until 1985, and Hepatitis C until 1990.[12] The National Hemophilia Foundation states that from the late 1970s into the 1980s about half of the individuals with hemophilia were infected with HIV related to blood product contamination, many of which died as a result of acquired immune deficiency syndrome (AIDS).[13]

Preoperative administration of Factor replacement is crucial for surgical hemostasis in the hemophiliac. The guidelines from the WFH include a detailed guide for Factor replacement according to surgical procedure. The recommended Factor VIII level for the hemophilia A patient undergoing minor surgery is 50- 80 % preoperatively, and 80-100 % preoperatively for major surgery. These levels are obtained with appropriate administration of Factor replacement; within the NUWIQ prescribing information the dose calculation is as follows:

Required IU = body weight (kg) x desired Factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL)

Expected Factor VIII rise (% of normal) = 2 x administered IU body weight (kg) [14]

Bleeding should be minimized in the intraoperative period in the presence of adequate Factor replacement and hemodynamic stability. Caution has been issued in respect to induction with succinylcholine as fasciculations could precipitate bleeding.[15, 16] Ensuring adequate depth of anesthesia to avoid airway

trauma has also been recommended.[15] In the presented case, a secondary venous access and an arterial line were considered appropriate. The WFH guidelines recommend avoiding intramuscular injections and treating the veins of a hemophilia patient with extreme care, because they are considered their lifeline (administration route of Factor replacement). [5] Early use of ultrasound can spare the patient multiple punctures; and the arterial access provides a manner to obtain intraoperative laboratory studies if needed. Range of motion should be documented preoperatively, and subsequent positioning of the patient should be conducted in light of that assessment.[17] Maintenance of anesthesia should include the avoidance of hypertension and tachycardia to minimize bleeding.[10]
Blood loss during the surgical procedure should be closely monitored and communicated between the surgical and anesthesia teams. An accurate, continuous monitoring of blood loss will help guide the anesthetist in anticipating additional treatments. The use of bypassing agents should be considered in the course of treatment in the patient with inhibitors. In the event that Factor VIII replacements are unavailable, desmopressin[18] and antifibrinolytics (epsilon aminocaproic acid, tranexamic acid[10]) have been used in certain scenarios. Side effects of both desmopressin and the antifibrinolytics must be considered before use. Desmopressin carries effects corresponding to the nature of a vasopressin analog, including both fluid retention and sodium disturbances. Hypotension with intravenous administration of desmopressin has also been reported. Disseminated intravascular coagulation (DIC) has been noted with the infusion of the antifibrinolytics.[18] Although blood products such as fresh frozen plasma (FFP) and cryoprecipitate contain the clotting factors deficient in hemophilia, they also maintain the risk of blood-borne infections which presents an increased risk in the patient with hemophilia and multiple infusion exposures.[5]
Monitoring postoperatively will be imperative as the patient with hemophilia is at risk for delayed bleeding at the surgical site (≥ 48 hrs after procedure).[18] Laboratory studies should be conducted and directed by the hematologist in regards to peak/trough levels of Factor VIII. These studies, in conjunction with physical assessment, will ensure that factor replacement is adequate. Early mobility and analgesia will also be key items to address in the post-operative period. The anesthesia provider must carefully weigh the risks and benefits of regional anesthesia, as studies have described successful use of regional anesthesia in the presence of adequate Factor replacement. [20] Other post-operative pain modalities include administration of opioids, acetaminophen[5], and COX-2 inhibitors, while the use of other non-steroidal anti-inflammatory agents is generally discouraged. [10,5] Monitoring beyond the perioperative period, one retrospective study found an increased risk of infection and blood transfusion among patients with coagulopathies (including hemophilia) in posterior lumbar fusions.[21]

Discussion

There are many limitations to studies that involve hemophilia A. Recent literature reviews[22,9] cite a common problem of minimal statistical power when attempting to draw conclusions for best practice in patients with hemophilia A in the perioperative setting. Literature available predominantly utilizes chart reviews and registries in retrospective analyses to document trends over time. The rare occurrence of the disease prohibits large effect size for controlled trials. Ethical concerns also exist, primarily because factor replacement is a largely safe and effective treatment in the patient with hemophilia A without inhibitors.
Anesthetic considerations for the patient with hemophilia A must be individualized to the patient, including disease severity and associated comorbidities. The risk of excessive bleeding must be recognized and managed with appropriate pharmacologic, surgical, and anesthetic techniques. Procedures should be conducted in a way that minimizes trauma, to reduce the risk bleeding from sources such as intubations, vascular access, and positioning. Accurate documentation of the patient's blood loss, medications received, and hemodynamic status will allow for comprehensive communication between providers and following the anesthetic. Special attention should be directed towards identification of delayed bleeding in the patient with hemophilia. Continued monitoring and specialized care (in conjunction with the hematologist) in the post-operative period will minimize the risk of additional bleeding.

Conclusion

Prompt recognition of the risks inherent to patients with hemophilia undergoing even minor procedures is paramount. For scheduled procedures, a plan of care and coordination with the multidisciplinary team (including a hematologist) should begin well before the day of surgery. The patient and family, who typically possess a high level of understanding of the disease, are an invaluable resource during this time as well. Effective communication between the care team members will ensure patient safety during the various stages of care. Adequate replacement of Factor VIII and recognition of inhibitors if present, are keys to anesthetic management in the patient with hemophilia A. Advances in healthcare now allow the patient with hemophilia to undergo major surgical procedures. Anesthesia providers that understand the pathophysiology of hemophilia A and the associated considerations will be equipped to minimize risk and promote safety in the perioperative period.

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Questions:

POST TEST

1. The deficient clotting factor in the patient with hemophilia A is:
   - A. Factor VIII
   - B. Factor III
   - C. Factor XII
   - D. Factor X

2. Common comorbidity associated with hemophilia A includes which of the following?
   - A. Hepatitis B
   - B. Joint dysfunction (i.e. arthropathy)
   - C. HIV/AIDS
   - D. All of the above

3. Anesthesia providers should avoid intramuscular injections in the patient with hemophilia A.
   - A. True
   - B. False

4. The estimated incidence of inhibitor development in the patient with hemophilia A is:
   - A. 10%
   - B. 20%
   - C. 4-30%
   - D. 25-50%

5. Before proceeding with major surgery, the recommended level of Factor VIII is:
   - A. 20-30%
   - B. 40-50%
   - C. 60-80%
   - D. 80-100%

6. Recombinant Factor VIII (i.e. NUWIQ) is administered by which of the following routes?
   - A. PO
   - B. IV
   - C. IM
   - D. Subcutaneous

7. A Factor VIII level of _____ constitutes severe hemophilia A.
   - A. < 1 %
   - B. 1-4%
   - C. 10%
   - D. 20%

8. Donated blood was not routinely screened for human immunodeficiency virus (HIV) until 1985.
   - A. True
   - B. False

9. Delayed bleeding (≥ 48 hours post-operatively) should not be a concern in the patient with hemophilia A.
   - A. True
   - B. False

10. Side effects of desmopressin can include
    - A. Sodium disturbances
    - B. Fluid retention
    - C. Hypotension
    - D. All of the above

11. Post-operative analgesia recommendations for the patient with hemophilia A include all of the following except:
    A. IV Acetaminophen
    B. Opioids
    C. COX-2 Inhibitors
    D. Toradol

12. Hemophilia was identified as early as the 2nd century.
    A. True
    B. False

13. The patient with hemophilia A with inhibitors may require which of the following:
    A. FEIBA
    B. Recombinant Activated Factor VII (rFVIIa)
    C. Increased dosing of recombinant Factor VIII
    D. All of the above

14. Multidisciplinary guidelines for the management of hemophilia are available from:
    A. The National Hemophilia Foundation
    B. The World Federation of Hemophilia
    C. Hemophilia Federation of America
    D. National Organization of Rare Disorders

15. In the event Factor VIII replacement is unavailable, desmopressin and antifibrinolytics have been used to supplement the patient with hemophilia A.
    A. True
    B. False

16. "Inhibitors" are thought to develop as a result of
    A. Previous Factor administration
    B. Patient immune response
    C. Length of Factor replacement treatment
    D. All of the above

17. Inhibitors are antibodies that neutralize Factor derivatives, and are associated with an increased risk of bleeding.
    A. True
    B. False

18. This induction medication should be administered with caution in the patient with hemophilia A:
    A. Propofol
    B. Opioids
    C. Midazolam
    D. Succinylcholine

19. Limitations of studies hemophilia A include the following:
    A. Small effect size
    B. Minimal statistical power
    C. Ethical concerns (effective treatment is already known)
    D. All of the above

20. Although cryoprecipitate and fresh frozen plasma include necessary clotting factors, blood products are sometimes avoided for the patient with hemophilia A because of:
    A. Risk of transfusion related illness
    B. Fluid balance concerns
    C. High cost
    D. Limited effectiveness

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